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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/612,921	07/10/2000	John E. Sims	03260.0047	9162

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EXAMINER
PRASAD, SARADA C

ART UNIT	PAPER NUMBER
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/612,921	Sims, John E	
	Examiner	Art Unit	
	Sarada C Prasad	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 November 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

kDetailed Action

1. Receipt of Applicants' arguments and amendments filed in Paper No. 11 (11/30/01) is acknowledged. Claims 13-41 have been cancelled, new claims 42-57 have been entered. Currently, claims 42-57 are under consideration.

2. The following previous rejections are withdrawn in light of Applicants' amendments filed in Paper No. 11 (11/30/01).

(i) rejection of claims 13 and 22 under 35 U.S.C. 112-second paragraph based on recitation of 'counterstructure molecules';

3. Applicant's arguments filed in Paper No. 11 (11/30/01), have been fully considered but were deemed persuasive in part. The issues remaining and new issues, are stated below. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Objections to claims:

4. Applicants make references to new claims 52-59 in their response in Paper No. 11 (page 10, 2nd para, lines 1-2; page 11 last para, line 1). However, claims currently being examined are new claims 42-57, and claims 58 and 59 are non-existent.

Claim Rejections - 35 USC § 101/112 first paragraph

5. Claims 42-57 remain rejected under 35 USC § 112 first paragraph as in Paper No. 7 (7/30/01).

This rejection of record is being maintained for reasons of record set forth in the previous office action (Paper No. 7, 7/30/01) as well as additional reasons stated below.

The specification sets forth a polynucleotide of SEQ ID No. 3 encoding a polypeptide of SEQ ID No. 4. When the human IL-1 delta amino acid sequence was compared to the mature form of the other IL-1 family members, it was found that it exhibited little identity with IL-1 alpha , 29% identity with IL-1 beta, 50% identity with IL-1ra, little identity with IL-18, 31% identity with IL-1 epsilon, and 34% with IL-1 zeta (specification page 9, entire 6th para). The disclosure also states that human IL-1 delta RNA expression can be detected in lymph node, thymus, tonsil, brain, placenta, lung, skeletal muscle, prostate, and testis (page 9, 2nd para, lines 1-2).

However, the instant 35 USC 101-utility rejection is based on the grounds that IL-1 delta polypeptides as described in the instant invention are proposed based on homology, and their specific use has not been established, but is contemplated. Statements such as, "it may act as an antagonist of other active cytokines, in the same way that IL-1ra is an antagonist of the action of IL-1 alpha and IL-1 beta" (page 10, 2nd para, lines 1-3) would support the Examiner's position of lack of established identity of the polypeptides. Additionally, the biological activity of the instant polypeptides is not disclosed. Specification directs to the meaning of biological activity as "IL-1delta protein is capable of associating with IL-1 delta counter structures or being co-immuno precipitated with IL-1 delta counterstructures or antibody to the IL-1 delta counter structure." (page 31 of specification, 2nd para). However, identification by antibodies or 'counterstrucutre molecules' of a polypeptide is not a specific biological activity, because no such counterstructures have been identified, and it is a truism that any protein can be precipitated with an antibody specific to it, and also because receptor or antibody binding can be due to partial identity of binding region or epitope(s) that is(are) common to other related proteins and

thus can bind with structurally similar proteins. Furthermore, the assay of IL-1 delta polypeptides either native polypeptides or variants is indicated to be based on binding to counterstructure molecules 'membrane bound receptors' or cells that contain the receptors and competition of such binding with IL-1 delta related molecules (page 35, 4th para). This evidence in the form of binding to antibodies and receptors without any subsequent endpoint to measure which occurs as a consequence of binding, fails to establish that the instant IL-1 delta polypeptides have utility other than binding because it is not known to one of skill in the art if the receptor-bound ligand has the potential of eliciting a measurable response characteristic of the IL-1 series of polypeptides or antagonize IL-1-like activities.

Extrapolation of function based on structural or sequence homology is not sufficient to establish utility. For example, art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech, 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see box 2, p 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p 399).

Response to Applicants' arguments in Paper No. 11:

Applicants' assert that IL-1 delta is useful for probes to identify nucleic acid encoding proteins having IL-1 delta activity (specification at page 36, lines 4-5). This argument is not persuasive, because the protein product, SEQ ID No. 4, of the instant nucleic acid of SEQ ID

NO. 3 has not been established to have biological activity, therefore it is not clear to one of skill in the art how use of such a probe would be able to identify additional nucleic acids encoding proteins having which 'activity of IL-1 delta'.

Applicants also assert that due to RNA expression pattern of IL-1 delta, probes based on the DNA sequence of SEQ ID No. 3 can be used to detect lymph node, thymus, tonsil, brain, placenta, lung, skeletal muscle, prostate, and testis tissue and cell types by methods such as in situ hybridization (lines 28-30 of page 36). However, this argument is not found persuasive because at a time when the expression of IL-1 delta RNA is detected in the several tissues listed by the Applicants, several additional RNAs are also expressed, and no conclusions can be drawn about the specificity of expression of IL-1 delta RNA, or the tissue type under consideration, or the utility of the instant nucleic acid as a tissue specific probe. Use of a polynucleotide as a tissue specific probe, or a chromosomal marker is not considered a specific and substantial utility, because almost every polynucleotide exhibits some tissue specific pattern of expression, and the results of such would not set forth any specific or substantial practical use for the pattern of expression of such polypeptides.

In addition, Applicants assert that all or portions of nucleic acids of SEQ ID NO. 2 including oligonucleotides, can be used to identify human chromosome 2, to analyze abnormalities associated with gene mapping to chromosome 2, to distinguish conditions in which this marker is rearranged or deleted, and a positional marker to map other genes of unknown location (Id. At page 37, lines 1-32) (page 5, entire 4th para of Paper No. 11, 11/30/01). Applicants also assert that in contrast to a general utility the instant asserted utility would be a specific utility because the instant polynucleotides can detect the 2q11-12 region of chromosome

2 or the specific RNA detected by the applicants. Additionally, applicants assert that IL-1 delta nucleic acid molecules discriminate alterations of 2q11-12 region of chromosome 2 from other chromosome alterations and to detect specific tissue and cell types are real world uses; and no further research is required. However, this utility is not specific because many oligonucleotides share chromosomal localization and can achieve similar results of serving as probes for mapping genes. Furthermore, the region of chromosome 2 that the Applicants point to as being the target of the instant nucleic acid, when used as a probe, is extremely large extending upto 92-110 megabases (see attachment of a map view of chromosome 2q11-2q12) and many probes such as SEQ ID NO. 3 would be equivalent to the instant probes in localizing to the region.

Based on the above discussion, the outstanding 35 USC 101-utility rejection of claims 42-57 is being maintained.

Claims 42-57 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either an asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

5b. Even if the specification, were enabling for the use of an isolated nucleic acid of SEQ ID No. 3 encoding a polypeptide of SEQ ID No. 4, it would not reasonably provide enablement for a nucleic acid molecule that encodes a fragment of the polypeptide of SEQ ID NO. 4, wherein the fragment binds to cells expressing an IL-1 delta receptor, or an isolated nucleic acid molecule that encodes a polypeptide that comprises an amino acid sequence that is at least 80% identical to SEQ ID NO. 4, wherein the polypeptide binds to cells expressing an IL-1 delta receptor, a

nucleic acid molecule that hybridizes to the nucleic acid molecules of SEQ ID No. 3 wherein said nucleic acid molecule is at least 90%, or 95%, or 98%, or 99% identical to SEQ ID NO. 3, or a nucleic acid molecules wherein the said nucleic acid molecule comprises at least 30 contiguous or 60 contiguous nucleotides of the nucleic acid molecule of SEQ ID NO. 3. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Claims 42, 46, 49, 52, 56, 57 are extremely broad. For example, recitation of an isolated nucleic acid molecule that encodes a fragment of the polypeptide of SEQ ID NO. 4, wherein the fragment binds to cells expressing an IL-1 delta receptor in claim 42 (b) encompasses all possible fragments of the polypeptide of SEQ ID No. 4. State of the art is such that 'a receptor binding fragment' is very precisely defined in several of the members of the interleukin family of cytokines. Guidance is not provided as to what are the criteria of such a receptor binding fragment to be made prior to testing for binding to counter structure molecules. The open claim language fails to set limits on the fragment length and recite delimiters, thus requiring undue experimentation to practice the claim as recited because one of skill in the art would not know

out of the 1-155 amino acid long SEQ ID No.4 which portion is included and not included in the fragment as recited in claim 42 (b).

The specification is non-enabling for the practice of claim 46 reciting isolated nucleic acid that encodes a polypeptide that comprises amino acids sequence with 80% identity to a polypeptide of SEQ ID NO. 4, because such IL-delta polypeptides could have up to 31 amino acids replaced out of the 155 amino acids of the IL-1 delta molecules, and such is expected to bind to cells expressing an IL-1 delta receptor. If one of skill in the art is allowed to alter up to 31 amino acid residues of SEQ ID NO. 4 without guidance, it would require undue experimentation to make and test such polypeptides that would have the intended utility. In order to prepare such extensively substituted, hypothetical polypeptides that can compete for receptor binding with IL-1 delta polypeptides guidance is required. The specification has failed to provide even one such variant that has been produced and used in the intended manner.

In a similar fashion, the specification also failed to disclose any examples of the claimed variants of SEQ ID No. 3 that would encode variants of SEQ ID No. 4 with 90-99% identity that might possess different binding affinities to receptors on cells which would offer reasonable expectation of success for a skilled artisan. Predictability in the art suggests how polypeptides with structural similarities are not necessarily functionally similar when it is not shown to be true. For example, Bork states most prediction schemes extrapolate from current knowledge, and many bioinformatics methods have difficulty exceeding a 70% prediction accuracy, while dealing with methods that deal with discrete objects such as sequences. In the instant case, the identity of the polypeptide of instant SEQ ID No. 4 to IL-1ra, at a 50% level, indicates that it is more like the receptor antagonist rather than IL-1α, or IL-1β, and this fact only points to

evolutionary relationship rather than establish its function either as an antagonist, or as an agonist. However, the specification has not provided any guidance as to what type of definite activity is expected of the instant SEQ ID NO. 4. Thus, if the expected activity of a polypeptide is not well defined, then the nucleic acid that encodes it would not be of substantial use as a probe for polynucleotides that encode for polypeptides. In fact, a post-filing date publication of the inventors themselves discloses a lack of minimum measurable activity, such as receptor binding, for the IL-1 delta polypeptides of the instant invention (Smith et al. 2000, J Biol chem. Vol. 275, page 1174, column 2, entire 1st para, Receptor binding).

Therefore, based on the above discussion, due to lack of guidance to prepare fragments of SEQ ID No. 4 that bind to receptors on cells, predictability in the art indicating how extensive amino acid replacements to obtain variant polypeptides can lead to polypeptides with unknown function, and due to the nature of the invention wherein specificity of receptor binding fragment resides in a defined region of the ligand, the instant claims 42-57 are rejected as not enabled for practice.

Response to applicants' arguments:

Applicant asserts that fragments of IL-1 delta can be made by many techniques well known in the art (pages 14-16 of specification) and assays for determining binding of IL-1 delta polypeptide fragments to IL-1 delta counter structures are described on pages 34-35 of the specification and consequently, generation of IL-1 delta fragments is predictable and does not require undue experimentation. Also, Applicant asserts that guidance for selection of polypeptide variants is provided in pages 17-24 of the specification and amino acid replacements are based on similar physicochemical characteristics (specification, page 18 , lines 12-18) (pages 9-10 of

Paper No. 11). The claims are drawn to a large number of different molecules, such as molecules with portions of sequences deleted, or added, or substituted, or also polypeptides encoded by the hybridization variants of the polynucleotide of SEQ ID No. 3. Considering the state of the art, it is possible for one of skill in the art to make such infinite number of different polynucleotides and polypeptides and test their binding, however, that is a task that requires undue experimentation, because there is no guidance regarding which of the infinite number of possible embodiments would predictably retain the function screened for. Additionally, the sequence features of hybridization variants of nucleic acids as recited in instant claims 42c and 52, and the unpredictable functionality of the consequent polypeptides generated from such nucleic acids are unpredicatable, and hence their use as probes or agonists or antagonists is unpredictable also.

Furthermore, Applicants assert that their written description of the claimed invention is adequate and the mere fact that something has not previously been done is not in itself a sufficient basis for rejecting all applications purporting to disclose how to do it (Page 11 of Paper No. 11). Applicant has merely extrapolated the function of the instant polypeptide of SEQ ID No. 4 based on 29%-50% homology and assumed enablement, while proposing utilities as agonists and antagonists without actually disclosing the competitive nature of such polypeptides. State of the art report of Skolnick et al. states that for proteins whose sequence identity is above 30%, one can use homology modeling to build the structure (page 36, column 2, 1st para, lines 1-3); however, knowing a protein's structure does not necessarily tell you its function (page 36, column 1, Box.2), because proteins can have similar folds but different functions.

Based on the above discussion, it is believed that all of applicant's arguments have been answered, however were not found persuasive, and therefore the instant 35 USC112-first paragraph rejection of claims 42, 46, 52, and 56 is maintained.

It is to be noted that the Examiner currently addressed the lack of sufficient written description requirement (Paper No. 8, 7/30/01) as part of scope of enablement requirement. Examiner's response to Applicants' arguments of rejection of claims based on lack of written description is also provided as part of maintaining the enablement rejection above.

Conclusion

7. No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sarada C Prasad whose telephone number is 703-305-1009. The examiner can normally be reached Monday – Friday from 8.00 AM to 4.30 PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for the organization where this application or proceeding is assigned is 703-308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Sarada Prasad, Ph.D.
Examiner
Art Unit 1646
February 4th , 2002

Yvonne Eyler
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